I. Remarks

Pursuant to the Examiner's request, Applicants will inform the Examiner of any errors in the specification should such errors become known to the Applicants. See, Paper No. 100505, page 2, comment 4.

Status of Claims

Applicants have amended claims 25, 37, and 48. Support for these amendments can be found at paragraphs 29-33 (pages 10-13) of the specification. Accordingly, no new matter has been added. Upon entry of the amendments submitted herein, claims 25-48 will currently be pending.

Amendment to the Specification and Sequence Listing

Please replace the Sequence Listing filed on December 12, 2003 in connection with the present application with the Substitute Sequence Listing enclosed herewith in written (two CDs labeled "Copy 1 Replacement 03/15/2006" and "Copy 2 Replacement 03/15/2006") and computer readable (one CD labeled "CRF Replacement 03/15/2006") forms.

Applicants have submitted herewith a Substitute Sequence Listing in order to list all of the inventors as requested by the Examiner, and as required under 37 CFR § 1.821-1.825. Applicants note that the Notice to Comply issued in the present office action contained incorrect Application No. and Applicant Information. Applicants have returned a copy of the Notice to Comply amended to show the correct information. Applicants have also inserted a new paragraph between paragraphs [0001] and [0002] of the specification to reference the substitute sequence listing submitted on compact disc, and properly indicate the labels and file creation date of the replacement compact discs, as required under 37 C.F.R. § 1.77(b)(4). Except for including a list of all inventors, the content of the substitute sequence listing is exactly the same as the original sequence listing filed on December 12, 2003. Applicants submit that no new matter has been added.

Change of Inventorship

The claims in the present application are drawn to HCE3C63 antibody embodiments. In this regard, the undersigned has been informed that the inventive entity of the subject matter encompassed by the elected claims is: D. Roxanne Duan, Steven M.

Ruben, and Craig A. Rosen. Accordingly, Applicants request that the present application be amended to show the above three persons as inventors. Thus, please remove the following names from the list of inventors: Michele Fiscella, Ping Wei, David W. LaFleur, Henrik S. Olsen, Kevin P. Baker, Reinhard Ebner, George A. Komatsoulis, Paul E. Young, Kimberly A. Florence, Paul A. Moore, Charles E. Birse, Jian Ni, Daniel R. Soppet, and Yanggu Shi.

II. Examiner Objections

Abstract

The Examiner objected to the abstract of the present disclosure as allegedly "not accurately describing [the] claimed invention." (See, Paper No. 100505, page 2, comment 5). Applicants respectfully disagree and traverse.

Applicants respectfully assert that the abstract of the present specification is a concise statement of the technical disclosure regarding the claimed invention that enables a reader, regardless of their familiarity with the background of the invention, to determine the nature of invention including what is new in the art to which the invention pertains. See M.P.E.P. (8th edition, revision 3) § 608.01(b). Nonetheless, in order to accommodate the Examiner's concerns, Applicants are willing to revise the abstract, however, more guidance in amending the abstract is respectfully requested.

Sequence Listing

Applicants have amended the sequence listing to include the listing of all inventors of the present application, as requested by the Examiner. Accordingly, Applicants respectfully request that the Examiner's objection to the sequence listing be reconsidered and withdrawn.

III. *Rejections of claims 25-48 under 35 U.S.C. § 101*

Claims 25-48 have been rejected under 35 U.S.C. § 101 for allegedly not being supported by "either a specific and substantial asserted utility, or a well-established utility." (See, Paper No. 100505, page 3, comment 9). Furthermore, the Examiner asserts: "the application is devoid of description of utility and working examples of the presently claimed protein function, which is neither clearly defined nor demonstrated." (See, Paper

No. 100505, page 4, last paragraph, comment 9). Applicants respectfully disagree and traverse this rejection.

As a preliminary matter, Applicants submit that the specification does assert a substantial and specific utility. In fact, the Examiner acknowledges that "[t]he specification also asserts that the protein [of the invention] can be used in diagnosing disease for example cancer, this asserted utility is substantial and specific, however, it is not credible." (See Paper No. 100505, page 4, second paragraph, comment 9). Accordingly, Applicants respectfully submit that rejection of claims 25-48 is not due to an alleged failure of Applicants to assert a specific and substantial utility, but rather because the asserted specific and substantial utility is allegedly not credible. Thus, Applicants respectfully request that the rejection of claims 25-48 under U.S.C. § 101 for allegedly not being supported by either a specific and substantial asserted utility or a well-established utility be withdrawn. Furthermore, Applicants respectfully disagree and traverse the Examiner's rejection of claims 25-48 under U.S.C. § 101 for allegedly not asserting a credible utility.

Applicants respectfully remind the Examiner that under section 2107.01 of the M.P.E.P. (8th edition, revision 3), credibility of a specific and substantial utility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record. In addition, the M.P.E.P. further states that "an applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy 35 U.S.C. 101 and 35 U.S.C. 112, additional statements of utility, even if not 'credible' do not render the claimed invention lacking in utility." (M.P.E.P. § 2107.02 at I. See also, M.P.E.P. § 2107 at II.B.(1)(ii)).

Applicants respectfully submit that the specific and substantial utility asserted by Applicants is credible, given the state of the art and the disclosure of the present application. For example, the specification discloses that HCE3C63 polypeptides, as well as antibodies raised against HCE3C63 polypeptides, are useful in the diagnosis, treatment, and/or prevention of several disorders, including brain cancer. *See* specification at pages 11-12, paragraph 32. In support of this assertion, the specification further discloses that HCE3C63 is "expressed primarily in different regions of the brain," (*See* specification at page 11, paragraph 30) and that HCE3C63 (SEQ ID NO:35) shares sequence homology with the tumor suppressor gene product, deleted in bladder cancer critical region 1 (DBCCR1). DBCCR1 encodes a putative 761 amino acid protein which when deleted or

when its promoter is hypermethylated (silenced), results in transitional cell carcinoma of the bladder. *See* Habuchi *et al.* (2001) and Nishiyama *et al.* (2001) submitted as references AQ and AR, on Applicants' Information Disclosure Statement submitted September 15, 2005.

In support of Applicants assertion that the utility of Secreted Protein HCE3C63, as a tumor suppressor, *i.e.*, a tumor diagnostic, is credible to one of skill in the art, Applicants respectfully submit that HCE3C63 shares several functional domains with DBCCR1. As evidenced in **Exhibit A**, both proteins have several phosphorylation sites (shaded), N-myristylation sites (in bold), N-glycosylation site (underlined) and a cysteine-rich region (boxed) in common over the length of their entire amino acid sequence. *See* Alignment submitted herewith as **Exhibit A**. *See* also **Exhibits B & C** (PROSITE analysis of HCE3C63 (SEQ ID NO:35) and DBCCR1 respectively; http://us.expasy.org/prosite). Since conserved protein domains and motifs represent evolutionary important structures, proteins sharing such conserved sequences likely have similar tertiary structures and possess similar functions. Accordingly, Applicants respectfully submit that one of skill in the art would conclude at the time the instant specification was filed that the assertion that HCE3C63 functions as a tumor suppressor like DBCCR1 is credible.

Therefore, a nexus exists between the sequence and functional domain homology of the present invention and DBCCR1; the specification's disclosure that HCE3C63 is specifically expressed in the brain; and Applicants' assertion that HCE3C63 is useful in the diagnosis, prevention, or therapy of brain cancer.

In addition, "to overcome the presumption of truth that an assertion of utility by the Applicant enjoys ... [it must be established] that one of ordinary skill in the art would doubt the truth of the statement of utility...To do this, [the Examiner] must provide evidence sufficient to show that the statement of asserted utility would be considered false by a person of ordinary skill in the art." See M.P.E.P. § 2107III(A) at 2139-40. Moreover, "an assertion [of utility] is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion [of utility] is based are inconsistent with the logic underlying the assertion." See M.P.E.P. § 2107(B) at 2100-40. However, in the instant rejection, the Examiner has not provided such reasoning or evidence.

In view of the above arguments, Applicants have provided evidence and reasoning which supports the Applicants' assertion of utility. In particular, Applicants have

provided evidence that the polypeptides and/or antibodies raised against the polypeptide of the instant application are useful as a cancer diagnostic. Accordingly, Applicants respectfully submit that the rejection of claims 25-48, under 35 U.S.C. § 101 has been obviated. Thus, Applicants respectfully request that the rejection of claims 25-48 be reconsidered and withdrawn.

IV. ***Rejections of claims 25-48 under 35 U.S.C. § 112***

The Examiner rejected claims 25-48 under 35 U.S.C. § 112, first paragraph because the claimed invention is allegedly "not supported by either a specific and substantial or a well established utility." (Paper No. 100505, page 4, comment 9). Applicants respectfully disagree and traverse.

Applicants respectfully submit that the Examiner "should not impose a 35 U.S.C. § 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. §101 rejection is proper." M.P.E.P. § 2107 (IV) at 2100-36. As discussed above, the claimed invention complies with the utility requirement of 35 U.S.C. § 101. Accordingly, Applicants respectfully request that the rejection of claims 25-48 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

V. ***Rejections of claims 25-33, 34, 35-44, 45, and 46-48 under 35 U.S.C. § 103(a)***

The Examiner rejected claims 25-33, 34, 35-44, 45, and 46-48 under 35 U.S.C. § 103(a) as being allegedly unpatenable over EMBL accession number AL035289 in view of Campell (ed.), Monoclonal Antibody Technology, 1985; 2nd Edition; Bost et al. Immunolgogical Investigations, 1988; 17:577-586; and Gavilondo et al. Biotechnique, 2000; 29:128-145. (Paper No. 100505, pages 4-6, comments 10-11). Applicants respectfully disagree and traverse.

As a preliminary matter, Applicants did not receive a copy of the sequence alignment between EMBL accession number AL035289 and SEQ ID NO:35 that was supposed to be attached to Paper No. 100505. See Paper No. 100505, page 5, comment 10. Nonetheless, Applicants have undertaken their own analysis and submit herewith a sequence alignment between EMBL accession number AL035289 and SEQ ID NO:35 as **Exhibit D**. Applicants urge the Examiner to examine Applicants' sequence alignment and inform Applicants if it significantly diverges from the sequence alignment recited by the Examiner on page 5 of Paper No. 100505.

In addition, Applicants respectfully submit that the priority date of the present application is November 2, 1999. Accordingly, Gavilondo et al. is not a proper reference under 35 U.S.C. § 103(a) since Gavilondo et al. was published in July 2000 (almost 8 months after the priority date of the present application).

Finally, Applicants have amended claims 25, 37, and 48 to recite the functional parameter "wherein said antibody or antibody fragment is useful for detecting or treating cancer." Since this use is not taught in the art cited by the Examiner, Applicants respectfully submit that these amendments obviate the Examiner rejections. Accordingly, Applicants respectfully request that the rejection of claims 25-33, 34, 35-44, 45, and 46-48 under 35 U.S.C. § 103(a) as being allegedly unpatenable over EMBL accession number AL035289 in view of Campell (ed.), Monoclonal Antibody Technology, 1985; 2nd Edition; Bost et al. Immunolgogical Investigations, 1988; 17:577-586; and Gavilondo et al. Biotechnique, 2000; 29:128-145, be reconsidered and withdrawn.

VI. Conclusion

Applicants respectfully request that the above-made amendments and remarks be entered and made of record in the present application. The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicant would expedite the examination of this application.

If there are any fees, not already accounted for, due in connection with the filing of this paper, please charge such fees to our Deposit Account No. 08-3425.

Date: March 20, 20006

Respectfully submitted,

By _____

Doyle A. Siever, Reg. No. 47,088
Patent Agent
HUMAN GENOME SCIENCES, INC.
Intellectual Property Department
14200 Shady Grove Road
Rockville, Maryland 20850
(301) 354-3932

KKH/DAS/DBS/ba

>gi|6857009 ref|NP_055433.1| (NM_014618) deleted in bladder cancer chromosome region candidate 1 [Homo sapiens]
Length = 761

Plus Strand HSPs:

Score = 2152 (762.6 bits), Expect = 6.4e-222, P = 6.4e-222
Identities = 408/777 (52%), Positives = 540/777 (69%), Frame = +3

```
SEQ 35:     1 MIWRSRAGAELFSLMALWEWIALS-LHCWVLAVAAVSDQHATSPFDWLLSDKGPFHRSQE 59
              M WR     EL    + +W  I++   H       A +DQH +  FDWL+SD+GPFH S+
DBCCR1:     1 MNWRF---VELLYFLFIWGRISVQPSH----QEPAGTDQHVSKEFDWLISDRGPFHHSRS 53

SEQ 35:    60 YTDFVDRSRQGFSTRYKIYREFGRWKVNNLAVERRNFLGSPLPLAPEFFRNIRLLGRRPT 119
              Y  FV+R RQGF+TRYKIYREF RWKV N A+ERR+ +  P+PL PEF R+IRLLGRRPT
DBCCR1:    54 YLSFVERHRQGFTTRYKIYREFARWKVRNTAIERRDLVRHPVPLMPEFQRSIRLLGRRPT 113

SEQ 35:   120 LQQITENLIKKYGTHFLLSATLGGEESLTIFVDKRKLSKRAEGSDSTTNSSSVTLETLHQ 179
               QQ  + +IKKYGTH L+SATLGGEE+LT+++DK +L ++   S + T S    +E LHQ
DBCCR1:   114 TQQFIDTIIKKYGTHLLISATLGGEEALTMYMDKSRLDRK---SGNATQS----VEALHQ 166

SEQ 35:   180 LAASYFIDRDSTLRRLHHIQIASTAIKVTETRTGPLGCSNYDNLDSVSSVLVQSPENKIQ 239
              LA+SYF+DRD T+RRLH IQI++ AIKVTETRTGPLGC++YDNLDSVSSVL+QS E+K+
DBCCR1:   167 LASSYFVDRDGTMRRLHEIQISTGAIKVTETRTGPLGCNSYDNLDSVSSVLLQSTESKLH 226

SEQ 35:   240 LQGLQVLLPDYLQERFVQAALSYIACNSEGEFICKENDCWCHCGPKFPECNCPSMDIQAM 299
              LQGLQ++ P YLQE+FVQ+ALSYI CN EGE++C+ + C C C  +FP+CNCP  DIQ M
DBCCR1:   227 LQGLQIIFPQYLQEKFVQSALSYIMCNGEGEYLCQNSQCRCQCAEEFPQCNCPITDIQIM 286

SEQ 35:   300 EENLLRITETWKAYNSDFEESDEFKLFMKRLPMNYFLNTSTIMHLWTMDSNFQRRYEQLE 359
              E  L  + ++W     D E SDEFK FMKRLP N+FL   +I   W  D + Q RY+ L+
DBCCR1:   287 EYTLANMAKSWAEAYKDLENSDEFKSFMKRLPSNHFLTIGSIHQHWGNDWDLQNRYKLLQ 346

SEQ 35:   360 NSMKQLFLKAQKIVHKLFSLSKRCHKQPLISLPRQRTSTYWLTRIQSFLYCNENGLLGSF 419
              ++ +    K Q+   KLF LS RC   P   LPR+RT   WL R+QS LYCNENG  G+F
DBCCR1:   347 SATEAQRQKIQRTARKLFGLSVRCRHNPNHQLPRERTIQQWLARVQSLLYCNENGFWGTF 406

SEQ 35:   420 SEETHSCTCPNDQVVCTAFLPCTVGDASACLTCAPDNRTRCGTCNTGYMLSQGLCKPEVA 479
               E   SC C      +C   +PC +G  ++C  C+  N + CG+CN GY L +G C+P+
DBCCR1:   407 LESQRSCVCHGSTTLCQRPIPCVIGGNNSCTMCSLANISLCGSCNKGYKLYRGRCEPQNV 466

SEQ 35:   480 ES--TDHYIGFETDL--QDLEMKYLLQKTDRRIEVHAIFISNDMRLNSWFDPSWRKRMLL 535
              +S  ++ +I FETDL  QDLE+KYLLQK D R+ VH  FISN++RL+++FDP WRKRM L
DBCCR1:   467 DSERSEQFISFETDLDFQDLELKYLLQKMDSRLYVHTTFISNEIRLDTFFDPRWRKRMSL 526

SEQ 35:   536 TLKSNKYKSSLVHMILGLSLQICLTKNSTLEPVLAVYVNPFGGSHSESWFMPVNENSFPD 595
              TLKSNK +   +HM++G+S++IC  +NS+L+P+  VYVNPF GSHSE W MP  E  +P.
DBCCR1:   527 TLKSNKNRMDFIHMVIGMSMRICQMRNSSLDPMFFVYVNPFSGSHSEGWNMPFGEFGYPR 586

SEQ 35:   596 WERTKLDLPLQCYNWTLTLGNKWKTFFETVHIYLRSRIKSNGPNGNESIYYEPLEFIDPS 655
              WE+ +L    QCYNWTL LGN+WKTFFETVHIYLRSR +      NE+    P++  DPS
DBCCR1:   587 WEKIRLQNS-QCYNWTLLLGNRWKTFFETVHIYLRSRTRLPTLLRNET-GQGPVDLSDPS 644

SEQ 35:   656 RNLGYMKINNIQVFGYSMHFDPEAIRDLILQLDYPYTQGSQ----DSALLQLLEIRDRVN 711
              +   Y+KI+++QVFGYS+ F+ + +R  + Q++  YTQG Q     S +L LL+IRDR+N
DBCCR1:   645 KRQFYIKISDVQVFGYSLRFNADLLRSAVQQVNQSYTQGGQFYSSSVMLLLLDIRDRIN 704

SEQ 35:   712 KLSPP---GQRRLDLFSCLLRHRLKLSTSEVVRIQSALQAFNAKLPNTMDYDTTKLC 766
              +L+PP   G+ +LDLFSC+L+HRLKL+ SE++R+  AL  +N ++    D  T KLC
DBCCR1:   705 RLAPPVAPGKPQLDLFSCMLKHRLKLTNSEIIRVNHALDLYNTEILKQSDQMTAKLC 761
```

Exhibit B

ScanProsite Results Viewer

This view shows ScanProsite results together with rule-based predicted features inside (profile) matches.

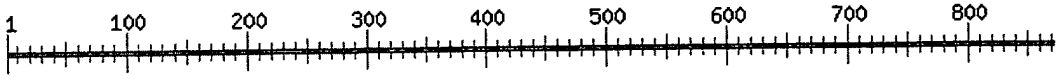
exclude splice variants; show hits of frequently occuring patterns

Hits for all PROSITE (release 19.20) motifs on sequence USERSEQ1 :

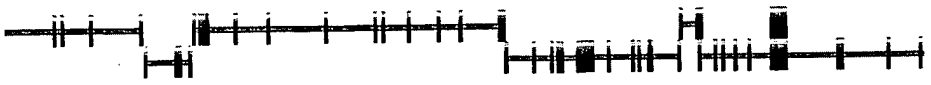
found: 43 hits in 1 sequence

USERSEQ1 (766 aa)

```
MIWRSRAGAELFSLMALWEWIALSLHCWVLAVAAVSDQHATSPFDWLLSDKGPFHRSQEYTDFVDR
SRQGFSTRYKIYREFGRWKVNNLAVERRNFLGSPLPLAPEFFRNIRLLGRRPTLQQITENLIKKYG
THFLLSATLGGEESLTIFVDKRKLSKRAEGSDSTTNSSSVTLETLHQLAASYFIDRDSTLRRLHHI
QIASTAIKVTETRTGPLGCSNYDNLDSVSSVLVQSPENKIQLQGLQVLLPDYLQERFVQAALSYIA
CNSEGEFICKENDCWCHCGPKFPECNCPSMDIQAMEENLLRITETWKAYNSDFEESDEFKLFMKRL
PMNYFLNTSTIMHLWTMDSNFQRRYEQLENSMKQLFLKAQKIVHKLFSLSKRCHKQPLISLPRQRT
STYWLTRIQSFLYCNENGLLGSFSEETHSCTCPNDQVVCTAFLPCTVGDASACLTCAPDNRTRCGT
CNTGYMLSQGLCKPEVAESTDHYIGFETDLQDLEMKYLLQKTDRRIEVHAIFISNDMRLNSWFDPS
WRKRMLLTLKSNKYKSSLVHMILGLSLQICLTKNSTLEPVLAVYVNPFGGSHSESWFMPVNENSFP
DWERTKLDLPLQCYNWTLTLGNKWKTFFETVHIYLRSRIKSNGPNGNESIYYEPLEFIDPSRNLGY
MKINNIQVFGYSMHFDPEAIRDLILQLDYPYTQGSQDSALLQLLEIRDRVNKLSPPGQRRLDLFSC
LLRHRLKLSTSEVVRIQSALQAFNAKLPNTMDYDTTKLCS
```

ruler: 

hits by patterns with a high probability of occurrence or by user-defined patterns: [43 hits (b

USERSEQ1  (766 aa

PS00006 **CK2_PHOSPHO_SITE** *Casein kinase II phosphorylation site* :

42 - 45: SpfD

218 - 221: SnyD

267 - 270: SegE

315 - 318: SdfE

418 - 421: SfsE

442 - 445: TvgD

523 - 526: SwfD

563 - 566: StlE

579 - 582: ShsE

592 - 595: SfpD

599 - 602: TklD

620 - 623: TffE

735 - 738: StsE

PS00005 **PKC_PHOSPHO_SITE** *Protein kinase C phosphorylation site* :

49 - 51: SdK

72 - 74: StR

157 - 159: SkR

191 - 193: TlR

309 - 311: TwK

361 - 363: SmK

380 - 382: SkR

504 - 506: TdR

528 - 530: SwR

536 - 538: TlK

539 - 541: SnK

761 - 763: TtK

PS00009 **AMIDATION** *Amidation site* :

114 - 117: lGRR

PS00004 **CAMP_PHOSPHO_SITE** *cAMP- and cGMP-dependent protein kinase phosphorylation site* :

116 - 119: RRpT

154 - 157: RKlS

PS00008 **MYRISTYL** *N-myristoylation site* :

142 - 147: GGeeSL

162 - 167: GSdsTT

414 - 419: GLlgSF

461 - 466: GTcnTG

577 - 582: GGshSE

694 - 699: GSqdSA

PS00001 **ASN_GLYCOSYLATION** *N-glycosylation site* :

168 - 171: NSSS

337 - 340: NTST

456 - 459: NRTR

562 - 565: NSTL

609 - 612: NWTL

641 - 644: NESI

PS00003 **SULFATION** *Tyrosine sulfation site* :

478 - 492:
vaestdhYigfetdl

638 - 652:
pngnesiYyeplefi

639 - 653:
ngnesiyYeplefid

Legend:

horizontal scaling: 0.6
do not show text labels:
do not show sites in hits:
do not show ranges in hits:
redisplay

Exhibit C

ScanProsite Results Viewer

This view shows ScanProsite results together with rule-based predicted features inside (profile) matches.

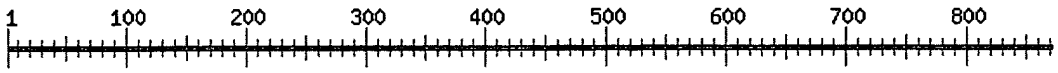
exclude splice variants; show hits of frequently occuring patterns

Hits for all PROSITE (release 19.20) motifs on sequence USERSEQ1 :

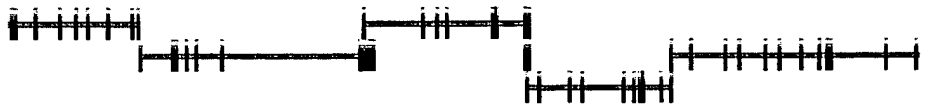
found: 43 hits in 1 sequence

USERSEQ1 (761 aa)

```
MNWRFVELLYFLFIWGRISVQPSHQEPAGTDQHVSKEFDWLISDRGPFHHSRSYLSFVERHRQGFT
TRYKIYREFARWKVRNTAIERRDLVRHPVPLMPEFQRSIRLLGRRPTTQQFIDTIIKKYGTHLLIS
ATLGGEEALTMYMDKSRLDRKSGNATQSVEALHQLASSYFVDRDGTMRRLHEIQISTGAIKVTETR
TGPLGCNSYDNLDSVSSVLLQSTESKLHLQGLQIIFPQYLQEKFVQSALSYIMCNGEGEYLCQNSQ
CRCQCAEEFPQCNCPITDIQIMEYTLANMAKSWAEAYKDLENSDEFKSFMKRLPSNHFLTIGSIHQ
HWGNDWDLQNRYKLLQSATEAQRQKIQRTARKLFGLSVRCRHNPNHQLPRERTIQQWLARVQSLLY
CNENGFWGTFLESQRSCVCHGSTTLCQRPIPCVIGGNNSCTMCSLANISLCGSCNKGYKLYRGRCE
PQNVDSERSEQFISFETDLDFQDLELKYLLQKMDSRLYVHTTFISNEIRLDTFFDPRWRKRMSLTL
KSNKNRMDFIHMVIGMSMRICQMRNSSLDPMFFVYVNPFSGSHSEGWNMPFGEFGYPRWEKIRLQN
SQCYNWTLLLGNRWKTFFETVHIYLRSRTRLPTLLRNETGQGPVDLSDPSKRQFYIKISDVQVFGY
SLRFNADLLRSAVQQVNQSYTQGGQFYSSSSVMLLLLDIRDRINRLAPPVAPGKPQLDLFSCMLKH
RLKLTNSEIIRVNHALDLYNTEILKQSDQMTAKLC
```

ruler: 

hits by patterns with a high probability of occurrence or by user-defined patterns: [43 hits (b

USERSEQ1  (761 aa)

PS00007 **TYR_PHOSPHO_SITE** *Tyrosine kinase phosphorylation site* :

4 - 10: Rfv.Ell.Y

PS00006 **CK2_PHOSPHO_SITE** *Casein kinase II phosphorylation site* :

23 - 26: ShqE

56 - 59: SfvE

83 - 86: TaiE

148 - 151: SrlD

296 - 299: SwaE

347 - 350: SatE

405 - 408: TflE

479 - 482: TdlD

514 - 517: TffD

554 - 557: SslD

570 - 573: ShsE

610 - 613: TffE

731 - 734: TnsE

PS00005 **PKC_PHOSPHO_SITE** *Protein kinase C phosphorylation site* :

43 - 45: SdR

66 - 68: TtR

104 - 106: SiR

178 - 180: TmR

359 - 361: TaR

367 - 369: SvR

409 - 411: SqR

468 - 470: SeR

527 - 529: TlK

530 - 532: SnK

545 - 547: SmR

644 - 646: SkR

661 - 663: SlR

757 - 759: TaK

PS00009 **AMIDATION** *Amidation site* :

108 - 111: lGRR

PS00004 **CAMP_PHOSPHO_SITE** *cAMP- and cGMP-dependent protein kinase phosphorylation site* :

110 - 113: RRpT

522 - 525: KRmS

PS00008 **MYRISTYL** *N-myristoylation site* :

136 - 141: GGeeAL

431 - 436: GGnnSC

432 - 437: GNnsCT

684 - 689: GQfySS

PS00001 **ASN_GLYCOSYLATION** *N-glycosylation site* :

156 - 159: NATQ

433 - 436: NNSC

443 - 446: NISL

553 - 556: NSSL

599 - 602: NWTL

631 - 634: NETG

677 - 680: NQSY

PS00003 **SULFATION** *Tyrosine sulfation site* :

294 - 308:
akswaeaYkdlensd

Legend:

horizontal scaling: 0.6
do not show text labels: ☐
do not show sites in hits: ☐
do not show ranges in hits: ☐
redisplay

Friday, February 10, 2006 11:09 AM
Lipman-Pearson Protein Alignment
Ktuple: 2; Gap Penalty: 4; Gap Length Penalty: 12

Exhibit D

Seq1(1>766) SEQ ID NO 35	Seq2(1>781) AL035289	Similarity Index	Gap Number	Gap Length	Consensus Length
(11>766)	(10>781)	70.0	4	16	772

```
          20        30                  40        50        60        70
LFSLMALW-EWIALSLHCWVLAV-----AAVSDQH----ATSPFDWLLSDKGPFHRSQEYTDFVDRSRQG
L  : :A W  . :AL:L. WVLAV      A.V::QH     :  P:DWLL:D:GPFHR:QEY:DF::R RQG
LRPAVAPWTALLALGLPGWVLAVSATAAAVVPEQHASVAGQHPLDWLLTDRGPFHRAQEYADFMERYRQG
 10        20        30        40        50        60        70
          80        90        100       110       120       130       140
FSTRYKIYREFGRWKVNNLAVERRNFLGSPLPLAPEFFRNIRLLGRRPTLQQITENLIKKYGTHFLLSAT
F:TRY:IYREF:RWKVNNLA:ER::F:: PLPLAPEF:RNIRLLGRRP.LQQ:TENLIKKYGTHFLLSAT
FTTRYRIYREFARWKVNNLALERKDFFSLPLPLAPEFIRNIRLLGRRPNLQQVTENLIKKYGTHFLLSAT
 80        90        100       110       120       130       140
          150       160             170       180       190       200
LGGEESLTIFVDKRKLSKRAE------GSDSTTNSSSVTLETLHQLAASYFIDRDSTLRRLHHIQIASTA
LGGEESLTIFVDK:KL::::E          ::::.NS::V:LETLHQLAASYFIDR:STLRRLHHIQIA:.A
LGGEESLTIFVDKQKLGRKTETTGGASIIGGSGNSTAVSLETLHQLAASYFIDRESTLRRLHHIQIATGA
 150       160       170       180       190       200       210
      210       220       230       240       250       260       270
IKVTETRTGPLGCSNYDNLDSVSSVLVQSPENKIQLQGLQVLLPDYLQERFVQAALSYIACNSEGEFICK
IKVTETRTGPLGCSNYDNLDSVSSVLVQSPENK:QL GLQVLLP:YL:ERFV.AALSYI:C:SEGE::CK
IKVTETRTGPLGCSNYDNLDSVSSVLVQSPENKVQLLGLQVLLPEYLRERFVAAALSYITCSSEGELVCK
 220       230       240       250       260       270       280
      280       290       300       310       320       330       340
ENDCWCHCGPKFPECNCPSMDIQAMEENLLRITETWKAYNSDFEESDEFKLFMKRLPMNYFLNTSTIMHL
ENDCWC.C:P.FPECNCP. DIQAME::LL:I ::W :.N.:FEES:EF: ::KRLP : FLN:::I ::
ENDCWCKCSPTFPECNCPDADIQAMEDSLLQIQDSWATHNRQFEESEEFQALLKRLPDDRFLNSTAISQF
 290       300       310       320       330       340       350
      350       360       370       380       390       400       410
WTMDSNFQRRYEQLENSMKQLFLKAQKIVHKLFSLSKRCHKQPLISLPRQRTSTYWLTRIQSFLYCNENG
W:MD:::Q:RY:QL.::K LF K:::I:::LF:L.KRCH:QP :.LP::R: :YW .RIQS:LYC.E:.
WAMDTSLQHRYQQLGAGLKVLFKKTHRILRRLFNLCKRCHRQPRFRLPKERSLSYWWNRIQSLLYCGEST
 360       370       380       390       400       410       420
      420       430       440       450       460       470       480
LLGSFSEETHSCTCPNDQVVCTAFLPCTVGDASACLTCAPDNRTRCGTCNTGYMLSQGLCKPEVAESTDH
: G:F E::HSCTCP DQ  C : :PC::G:::AC  CAPDN.TRCG:CN.GY:L:QGLC:PEVAES ::
FPGTFLEQSHSCTCPYDQSSCQGPIPCALGEGPACAHCAPDNSTRCGSCNPGYVLAQGLCRPEVAESLEN
 430       440       450       460       470       480       490
      490       500       510       520       530       540       550
YIGFETDLQDLEMKYLLQKTDRRIEVHAIFISNDMRLNSWFDPSWRKRMLLTLKSNKYKSSLVHMILGLS
::G:ETDLQDLE:KYLLQK D.RIEVH:IFISNDMRL.SWFDPSWRKRMLLTLKSNKYK::LVH::L:LS
FLGLETDLQDLELKYLLQKQDSRIEVHSIFISNDMRLGSWFDPSWRKRMLLTLKSNKYKPGLVHVMLALS
 500       510       520       530       540       550       560
      560       570       580       590       600       610       620
LQICLTKNSTLEPVLAVYVNPFGGSHSESWFMPVNENSFPDWERTKLDLPLQCYNWTLTLGNKWKTFFET
LQICLTKNSTLEPV:A:YVNPFGGSHSESWFMPVNE.SFPDWERT::D : QC NWT:TLGN:WKTFFET
LQICLTKNSTLEPVMAIYVNPFGGSHSESWFMPVNEGSFPDWERTNVDAAAQCQNWTITLGNRWKTFFET
 570       580       590       600       610       620       630
      630       640       650       660       670       680       690
VHIYLRSRIKSNGPNGNESIYYEPLEFIDPSRNLGYMKINNIQVFGYSMHFDPEAIRDLILQLDYPYTQG
VH:YLRSRIKS :  ::NE:IYYEPLE..DPS:NLGYMKIN.:QVFGYS:.FDP:AIRDLILQLDYPYTQG
VHVYLRSRIKSLDDSSNETIYYEPLEMTDPSKNLGYMKINTLQVFGYSLPFDPDAIRDLILQLDYPYTQG
 640       650       660       670       680       690       700
```

Lipman-Pearson Protein Alignment
Ktuple: 2; Gap Penalty: 4; Gap Length Penalty: 12

Seq1(1>766) SEQ ID NO 35	Seq2(1>781) AL035289	Similarity Index	Gap Number	Gap Length	Consensus Length
(11>766)	(10>781)	70.0	4	16	772

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      700       710       720       730       740       750       760
SQDSALLQLLEIRDRVNKLSPPGQRRLDLFSCLLRHRLKLSTSEVVRIQSALQAFNAKLPNTMDYDTTKL
SQDSALLQL:E:RDRVN:LSPPG: RLDLFSCLLRHRLKL:.:EV RIQS:L:AFN:KLPN.::Y:T.KL
SQDSALLQLIELRDRVNQLSPPGKVRLDLFSCLLRHRLKLANNEVGRIQSSLRAFNSKLPNPVEYETGKL
 710       720       730       740       750       760       770

CS
CS
CS
 780
```